REMARKS

Claims 39-42, 44, 46-64 and 77-98 are presently pending. Claims 39, 40, 44, 46, 82, and 88 are amended herein. No new matter has been introduced by way of this amendment.

I. Claims 39-42, 44, 46-64, and 77-98 are enabled by the specification.

Claims 39-42, 44, 46-64 and 77-98 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants traverse the rejection because those skilled in the art at the time of filing of the present application having Applicant's disclosure available to them would have been able to make and use the gene-targeted rodent as defined by the solicited claims without undue experimentation.

The first paragraph of section 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The test of enablement is **not** simply whether experimentation would have been necessary, but whether such experimentation would have been **undue**. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and

viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of non-enablement must be based on the evidence as a whole. *Id.*

When rejecting a claim under the enablement requirement of section 112, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why [it] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *See id.*; MPEP § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *See In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

Applicants note that the Examiner agrees the specification is enabling for "a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rodent comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse." Office Action at 2-3. Accordingly, Applicants submit that claim 78 should not be included in the rejection.

The reasons asserted for the alleged lack of enablement of the full scope of the claims apparently are four-fold: first, it is alleged that the specification does not enable a gene-targeted mouse having the PS-1 P264L mutation manifesting any effect on murine Aβ42

levels or AD phenotypes (Office Action at 6-7); second, the Examiner alleges that the specification is not enabling for mice having human presenilin-1 (PS-1) FAD mutations in addition to P264L (Office Action at 4); third, the Examiner asserts that only a gene-targeted mouse heterozygous for the PS-1 and APP mutations are enabled (Office Action at 2-3); and fourth, the Examiner alleges that the specification is not enabling for the genus of rodents (Office Action at 4). Applicants will address each of these grounds for the rejection in turn.

A. *The specification teaches the effect of a human PS-1 FAD mutation in mice.*

The Examiner asserts that "the specification provides limited guidance on page 5 with regard to phenotypic expression of the P264L mutation. The specification indicates that the P264L mutation in humans caused an increased amount of amyloid A-beta42 protein, and is involved in clinical manifestation of Alzheimer's Disease (AD). However, neither the specification nor its incorporated references provides any teaching on any biological effect on the amount of murine amyloid A-beta42 expression or clinical manifestation of AD in the mouse of the invention." Office Action at 6-7. Applicants disagree.

Applicants first invite the Examiner's attention to the definition of the phrase "human mutation in the non-human mammalian presenilin-1 (PS-1) FAD gene" provided in the specification. As defined therein, that phrase means any mutation of the PS-1 gene in a non-human mammal that results in the non-human mammal having a nucleotide or nucleotides that *correspond to* the human PS-1 gene at the corresponding position of the nucleotide or nucleotides. *See* Specification at 10. Accordingly, Applicants are not merely introducing an exogenous mutated human PS-1 gene into rodents but rather are introducing a mutation associated with FAD in humans into the mouse PS-1 gene. *See* Specification at 5-6. While PS-1$^{P264L/P264L}$ mice do not exhibit deposits at 12 months of age (*see* Specification at 39,

Example 8), mice expressing mutant PS-1 exhibit elevated levels of Aβ1-42 (*see* Specification at 4). Applicants have demonstrated that Tg2576 x PS-$1^{P264L/P264L}$ mice and $APP^{NLh/NLh}$ x PS-$1^{P264L/P264L}$ mice exhibit elevated Aβ42 levels (*see* Specification at 37, Tables 2 and 3), increased Aβ42/Aβ40 ratios (*see id.*), and accelerated rates of deposition (*see* Specification at 38, Table 4). Accordingly, Applicants submit that the ordinarily skilled artisan would understand the biological effect of a human PS-1 FAD mutation, such as P264L, in rodents. Applicants have taught the effect of a PS-1 FAD mutation, both alone and in combination with a human Swedish APP mutation, on Aβ42 peptide levels, Aβ42/Aβ40 ratios, and Aβ deposition in rodents. Applicants have provided extensive guidance on the biological effect of a human PS-1 FAD mutation in rodents.

Additionally, Applicants note that claims 39-42, 44, 46, and 77-88 require that the claimed rodent exhibit an elevated Aβ42 protein level relative to that of a wild-type mouse.

The Examiner maintains that the specification allegedly does not provide sufficient guidance for producing rodents having FAD phenotypic traits, specifically the pathology and symptomatology of ADA. *See* Office Action at 8. The Examiner's reasoning is misplaced. Applicants do not claim gene-targeted rodents exhibiting symptoms of ADA. Rather the phrase "human Familial Alzheimer's Disease (FAD) mutation" refers to the ***genetic composition*** of the claimed rodents. Specifically, the claimed rodent is hetero- or homozygous for a human FAD mutation comprising a human mutation of the PS-1 gene. Applicants thoroughly detail methods of making and using the claimed rodents, for example, by providing numerous working examples. One having ordinary skill in the art would have been able to make and use a gene-targeted rodent that is hetero- or homozygous for a human FAD mutation comprising a human mutation of the PS-1 gene using Applicants' disclosure as a guide.

The Examiner's reference to claims 58-60 is inapposite as those claims encompass methods for identifying compounds for treating Alzheimer's Disease, not rodents exhibiting symptoms thereof. Applicants have enabled method steps requiring measurement of the deposits of Aβ peptide in a tissue sample of a rodent. For example, Applicants teach the stereological determination of the volume of neocortex and percent volume of neocortex of a rodent occupied by Aβ deposits by point counting. *See, e.g.,* Specification at 38.

Accordingly, Applicants request reconsideration and withdrawal of this ground of rejection for alleged lack of enablement.

B. *The specification enables rodents having human PS-1 FAD mutations in addition to P264L.*

The Examiner asserts that "[t]he specification (pages 37-39) coupled with knowledge in the prior art provides sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention directed to [a] gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation . . . ." Office Action at 3. Applicants agree but assert that the specification further enables gene-targeted rodents having PS-1 mutations in addition to the PS-1 P264L mutation.

Applicants submit that the Examiner has not set forth the requisite evidence to support a *prima facie* case of lack of enablement of claims encompassing gene-targeted rodents having a PS-1 mutation other than P264L, generational offspring thereof, and their methods of use. To object to a specification on the grounds that the disclosure is not enabling with

respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *See In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); MPEP § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *See In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). In the present case, the Examiner has presented no support for the assertion that PS-1 mutations other than those of the examples would not work in the invention. Applicants request that the Examiner provide such support or withdraw the rejection.

Moreover, it is well-established that an applicant for a patent is not required to disclose every species encompassed by the claims. *See Enzo Biochem v. Calgene*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). Rather, applicant's disclosure need only teach those of ordinary skill to make and use the invention as it is claimed. *See id.* Further, the specification need only disclose one mode of making and using a claimed invention to satisfy the enablement requirement. *See Amgen v. Hoechst Marion Roussel*, 2003 U.S. App. LEXIS 118 at *50 (Fed. Cir. Jan. 6, 2003).

In the present case, Applicants provide more than 70 examples of human mutations in the non-human mammalian PS-1 FAD gene, of which P264L is just one. *See* Specification at 10-12. The specification provides a number of working examples of the mutated PS-1 FAD gene having the P264L mutation. The specification clearly teaches that P264L is a representative example of the numerous other PS-1 mutations encompassed within the scope of the claims. *See, e.g.,* Specification at 12 ("Although the application exemplifies the P264L mutation in particular, all aspects of the invention can be applied to each and every human mutation recited above."). Applicants have extensively detailed the construction of a targeting vector having a human PS-1 FAD mutation (*see, e.g.,* Specification at 22-27,

Example 2; Figures 13-18), the establishment of transformed ES cells and mutant mice hetero- and homozygous for the human PS-1 FAD mutation (*see, e.g.,* Specification at 27-32, Examples 3-5), and analysis of Aβ peptide levels and deposition therein (*see, e.g.,* Specification at 33-39, Examples 7-8). One having ordinary skill in the art would have recognized that the methods of the examples of Applicants' disclosure are equally applicable to human PS-1 FAD mutations other than P264L. Nothing more than routine experimentation was required to substitute another human PS-1 FAD mutation for P264L in Applicants' methods. Accordingly, the human PS-1 FAD mutations encompassed by the solicited claims are fully enabled by Applicants' disclosure.

C. *Claims encompassing rodents homozygous for the recited mutations are enabled by the specification.*

The Examiner limits the acknowledgment of enabled subject matter to mice heterozygous for the recited PS-1 and/or APP mutations. *See* Office Action at 2. Applicants submit that, in addition to rodents heterozygous for the recited mutations, Applicants' specification enables rodents homozygous for such mutations.

Applicants submit that the Examiner has not set forth the requisite evidence to support a *prima facie* case of lack of enablement in this regard. To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *See In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); MPEP § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *See In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). In the present case, the Examiner has

presented no reasoning for asserting that rodents homozygous for the recited mutations are not enabled. Applicants request that the Examiner either provide such support or acknowledge enablement of rodents homozygous for the recited mutations.

Applicants assert that rodents homozygous for PS-1 and APP mutations are likewise enabled. Applicants teach that rodents homozygous for PS-1 and/or APP mutations are generated by cross-breeding heterozygous rodents. *See, e.g.,* Specification at 32, Example 5. For example, Applicants demonstrated that mice homozygous for the PS-1 ^{nP264L} allele are generated by first cross-breeding mice heterozygous for that allele and homozygous for a humanized APP gene. *See id.* Genotyping analysis is used to demonstrate the presence or absence of a given allele. *See id.* (describing a PCR-based genotyping analysis); *see also* Figure 19 (depicting a strategy for detecting homologous recombination within a rodent PS-1 gene). Generational offspring heterozygous for PS-1 P264L and APP695 were subsequently cross-bred, thereby yielding mice having the following genotypes: PS-1$^{P264L/P264L}$ x APP$^{NLh/+}$; PS-1$^{P264L/+}$ x APP$^{NLh/+}$; PS-1$^{P264L/+}$ x APP$^{NLh/NLh}$; and PS-1$^{P264L/P264L}$ x APP$^{NLh/NLh}$. The ordinarily skilled artisan, using Applicants' disclosure as a guide, would have been able to generate and genotype rodents homozygous for the PS-1 P264L allele and/or the humanized APP allele without undue experimentation. Accordingly, Applicants have satisfied the requirements for enablement.

D. *Claims encompassing gene-targeted rodents are enabled by the specification.*

It is additionally alleged that Applicants have not enabled the full scope of their claims with respect to the claimed genus of rodents. *See* Office Action at 7-8. Applicants disagree.

The Examiner seems to rely on two lines of reasoning in this regard. First, the

Examiner asserts that the art of transgenics is unpredictable. The Examiner cites Palmiter et al. (1991), Wall, Whitelaw et al., and Palmiter et al. (1986) to support this assertion. The Examiner further asserts that there is a lack of reasonable correlation between rodent and other species in ES technology, relying on Polejaeve et al. and Rulicke et al. as support therefor.

1. *Palmiter et al. (1991), Wall, Whitelaw et al., and Palmiter et al. (1986) are inapposite.*

The Examiner cites Palmiter et al. (1991), Wall, Whitelaw et al., and Palmiter et al. (1986) to support the alleged unpredictability of transgenic technology. *See* Office Action at 5. Applicants assert that the cited references are irrelevant to the enablement of the claimed gene-targeted rodents of the present invention.

Applicants do not employ transgenic technology in the invention. As explained in the specification, genetic engineering can be accomplished by two distinct approaches: (1) a transgenic approach where an exogenous gene is randomly inserted into the host genome, and (2) a gene-targeting approach where a specific endogenous gene is partially or completely removed or replaced by homologous recombination. *See* Specification at 4. The present invention employs the latter technique. As a result, the presenilin-1 protein in the gene-targeted rodents of the invention is expressed with the same developmental timing, tissue specificity, and rates of synthesis normally associated with native presenilin-1 protein in the wild-type rodent. *See* Specification at 9.

Palmiter et al. (1991) teaches that "[t]he two most common problems [with transgenic technology] are inappropriate expression patterns and failure to achieve adequate expression levels." Palmiter et al. (1991) at 478. As previously noted, Applicants acknowledge these limitations of transgenic technology and, therefore, employ gene-targeting methods to avoid

them.

Wall describes the unpredictability of transgene behavior due to unidentified control elements and "position effect." Wall at 61-62. Specifically, because the transgene inserts randomly in the genome, it may land near highly active endogenous genes or in transcriptionally inactive regions, thereby leading to aberrant expression. *See id.* Again, Applicants acknowledged this limitation of transgene technology and accordingly developed a gene-targeting approach, wherein the mutant gene inserts at the endogenous genomic site and is subject to endogenous control elements, thereby avoiding the position effect described by Wall.

Whitelaw et al. describes experimental results suggesting that some or all natural introns may be necessary for efficient expression of a given transgene. Applicants, however, do not employ transgenic technology. Rather, Applicants claim *gene-targeted* rodents. As the targeting vector employed by Applicants' protocol replaces at least a portion of an exon of the endogenous gene, for example exon 8 of the PS-1 gene (*see, e.g.,* Specification at 14), with the mutated version thereof, the introns may be left intact. Accordingly, the limitations of transgenic technology noted by Whitelaw et al. are irrelevant to the enablement of the solicited claims.

Similarly, shortcomings of transgenic technology, including variable expression are described by Palmiter et al. (1986). *See* Palmiter et al. at 482-483. That reference, however, cites the position effect of transgenic technology as the likely reason for variable expression. *See id.* at 483 (explaining that integration of the transgene at different chromosomal locations where activation or commitment is variable causes variable expression). As the present invention employs gene targeting rather than transgenic technology, this limitation of the latter art is irrelevant to the enablement of the solicited claims.

As no *prima facie* case of lack of enablement has been established on this record on the basis of shortcomings of transgenic technology, Applicants request reconsideration and withdrawal of the rejection.

2. *ES technology is available in rodents.*

Polejaeva et al., Rulicke et al., and Bishop are cited as support for the Examiner's allegation that Applicants' disclosure does not enable the claimed genus of gene-targeted rodents due to a lack of correlation between ES technology of the mouse and other rodents. Applicants disagree.

The passage of Polejaeva et al. to which the Examiner refers addresses pronuclear injection. In regard to gene targeting in embryonic stem cells, however, Polejaeva et al. reports that ES cells may be derived from mammalian embryos. *See Polejaeva et al.* at 119-120. Accordingly, Polejaeva does not support an allegation of lack of enablement of the solicited claims.

The Examiner further cites Rulicke et al. and Bishop for the proposition that ES technology is limited to the mouse and that at present only putative ES cells exist for other species. *See* Office Action at 6. This assertion is rebutted by numerous references, such as Thomson et al. (*Proc. Natl. Acad. Sci. USA*, 92:7844-7848 (1995)) (stating that well-characterized ES cells have been derived from rodents); Doetschman et al. (*Dev. Biol.*, 127:224-227 (1988)) (describing hamster ES cells); and Iannaccone et al. (*Dev. Biol.*, 163:288-292 (1994)) (describing rat ES cells). Courtesy copies of the cited references are submitted herewith for the Examiner's convenience.

As the ordinarily skilled artisan would have known that ES cell technology is available in rodents and is not limited to mice, Applicants submit the solicited claims a re

fully enabled.

II. Claims 39-42, 44, 46-64, and 77-98 are patentable over the cited references.

Claims 39-42, 44, 46-64, and 77-98 are rejected under 35 U.S.C. § 103 for alleged obviousness over U.S. Patent No. 5,898,094 (hereinafter "Duff et al.") in view of U.S. Patent No. 5,850,003 (hereinafter "McLonlogue et al."). Applicants traverse.

To establish a *prima facie* case of obviousness, three requirements must be satisfied: first, there must be some suggestion or motivation to modify the reference or to combine the reference teachings; second, there must be a reasonable expectation of success for achieving the claimed invention and its particular results; and, third, the prior art references must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

Claims 39, 41, 44, 77-82, and 97 encompass gene-targeted rodents heterozygous for a human FAD mutation comprising a human mutation of the PS-1 gene and a human transgene for Swedish APP695, wherein the Aβ42 protein level is elevated relative to wild-type. Similarly, claims 40, 42, 46, 83-88, and 98 recite gene-targeted rodents homozygous for a human FAD mutation comprising a human mutation of the PS-1 gene and a human transgene for Swedish APP695, wherein the Aβ42 protein level is elevated relative to wild-type. Claims 47 and 48 are directed to generational offspring thereof wherein the mutant PS-1 gene is expressed. Methods for screening chemical compounds for the ability to decrease *in vivo* levels of the Aβ peptide by administering a compound to a gene-targeted rodent of the invention and measuring the amount of Aβ peptide therein, wherein a decrease in Aβ peptide is indicative of a chemical compound that has the ability to decrease *in vivo* levels of Aβ

peptide, are encompassed by claims 49-56 and 89-96. Claims 57-64 are directed to similar methods for identifying a compound for treating AD.

Duff et al. describes transgenic mice having PS-1 M146L and APP695 transgenes. As acknowledged by the Examiner, however, Duff et al does not teach the use of gene targeting to produce the mice described therein. The Examiner relies on McLonlogue et al. for the alleged teaching of gene targeting the PS-1 gene in combination with the transgenic mouse described by Duff et al. to yield the gene-targeted rodent of the present invention.

Preliminarily, the test of whether a prior art reference may be relied upon to show that the claimed subject matter at issue would have been obvious is whether the prior art provided an enabling disclosure with respect to the claimed subject matter. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281 (Fed. Cir. 1985); *see also* MPEP § 2121.01. Applicants assert that neither McLonlogue et al. nor Duff et al. provides an enabling disclosure for making or using a gene-targeted rodent having a human PS-1 FAD mutation. McLonlogue et al. describes only methods for generating a gene-targeted mouse having an APP mutation. That reference, however, provides no guidance or working examples for producing a rodent having a PS-1 FAD mutation by gene targeting. Accordingly, one having ordinary skill in the art could not have generated the rodent of the invention using Duff et al. and McLonlogue et al. as a guide without undue experimentation. Applicants therefore request reconsideration and withdrawal of the rejection.

Additionally, even the cited combination of references does not teach every element of the solicited claims. Neither Duff et al. nor McLonlogue et al. teaches or suggests, either expressly or inherently, a rodent having a gene-targeted human PS-1 FAD mutation and APP695 transgene that exhibits elevated Aβ42 levels relative to wild-type as set forth in claims 39-42, 44, 46, 77-88, 97, and 98. Duff et al. only describes accelerated rates of Aβ

deposition (*see, e.g.,* Duff et al. at column 9, lines 50-55; Table 1) and elevated Aβ1-42 levels of the transgenic mice set forth therein (*see, e.g.,* Duff et al. at column 9, lines 50-55). While McLonlogue et al. describe increased levels of Aβ peptide in the APP mutant mice presented therein, which Aβ peptide level is elevated is not disclosed. The phenotype of a PS-1/APP695 double mutant rodent with respect to Aβ42 levels would not have been obvious to the ordinarily skilled artisan in view of Duff et al. or McLonlogue et al. Accordingly, even the combination of the cited references does not amount to the present invention as defined by claims 39-42, 44, 46, 77-88, 97, and 98.

Additionally, neither Duff et al. nor McLonlogue et al. teaches or suggests, either expressly or inherently, generational offspring of the gene-targeted rodents having the gene-targeted manipulation of the PS-1 gene of the parents as set forth in claims 47 and 48 or methods for identifying a compound for treating AD or having the ability to decrease *in vivo* levels of Aβ peptide of claims 49-64 and 89-96 using the rodents of the invention. Accordingly, even the combination of the cited references does not amount to the present invention as defined by those claims.

Applicants request reconsideration and withdrawal of the rejection.

III. Response to the obviousness-type double patenting rejection

Claims 39-42, 44, 46-64, and 77-98 are rejected for alleged obviousness-type double patenting over claims 1-10 of U.S. Patent No. 6,284,924 in view of Duff et al. and claims 1-4 of McLonlogue et al. Preliminarily, Applicants note that U.S. Patent No. 6,284,924 is irrelevant to the present analysis. Applicants submit that the correct number of the patent being asserted as the basis for the rejection is previously cited U.S. Patent No. 6,284,944.

Although Applicants disagree, Applicants will file a Terminal Disclaimer upon receipt of an indication of allowable claims.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-557-5908.

Respectfully submitted,

Date: March 10, 2003

Felicity E. Groth
Registration No. 47,042

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Attachment(s):

Version with Markings to Show Changes Made
Thomson et al. (*Proc. Natl. Acad. Sci. USA*, 92:7844-7848 (1995))
Doetschman et al. (*Dev. Biol.*, 127:224-227 (1988))
Iannaccone et al. (*Dev. Biol.*, 163:288-292 (1994))

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend claims 39, 40, 44, 46, 82, and 88 as follows:

39. (Twice Amended) A gene-targeted[, non-human] rodent heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human [transgenic] transgene for Swedish APP695, wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.

40. (Twice Amended) A gene-targeted[, non-human] rodent homozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human [transgenic] transgene for Swedish APP695, wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.

44. (Twice Amended) The rodent of claim [43] 39 wherein said rodent is a mouse.

46. (Twice Amended) The rodent of claim [45] 40 wherein said rodent is a mouse.

82. (Amended) A generational offspring of the [mouse] rodent of claim 77 wherein said offspring comprises in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.

88. (Amended) A generational offspring of the [mouse] rodent of claim 83 wherein said offspring comprises in its genome:

a DNA sequence encoding a PS-1 protein comprising the human P264L mutation; and

a DNA sequence encoding a human amyloid precursor protein having the Swedish APP695 mutation;

wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.